REMARKS

Applicants respectfully request reconsideration of this application in view of the foregoing amendments and the following remarks.

I. Status of the Claims

Upon entry of the foregoing amendments, claims 1 and 44-99 will remain pending in the application. Claims 1, 44-55, 63-76 and 84-85 are under examination, while claims 56-62, 77-83 and 86-99 are withdrawn from consideration.

Claims 1 and 64 are amended to specify that the recited immunogenic complex does not comprise alum. Support for this embodiment is found, for example, at page 26, line 19, of the application as filed.[1] Applicants respectfully request entry of these amendments after final because they are believed to place the application in condition for allowance or, at the very least, in better condition for appeal. Moreover, they should not require a new search.

II. The Claimed Invention is Novel

Claims 1, 46-55, 64, 66-76 and 85 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by WO 98/15287A1 ("Garcon I"). Applicants respectfully traverse these rejections.

The rejected claims are directed to "an immunogenic complex comprising a negatively charged organic complex and a charged antigen, which organic complex and antigen are electrostatically associated," and to compositions comprising such a complex. As noted previously, Garcon I fails to teach or suggest such complexes because there is no electrostatic association between the organic carrier and antigen of Garcon I. While Applicants explained this difference between the claimed invention and Garcon I with reference to the method by which the Garcon I compositions are made (*e.g.*, in Garcon I, the antigen is adsorbed to alum before the addition of MPL or QS21, Garcon I, page 7, lines 15-24), Applicants emphasize that the difference is embodied in the compositions *per se*. Thus,

[1] As noted in MPEP 2173.05(i), "[i]f alternative elements are positively recited in the specification, they may be explicitly excluded in the claims."

the dismissal of this difference because "the argument of different methods of making the claimed composition does not encompass the [composition] claims," Office Action, page 2, was incorrect and improper.

As explained at page 11 of the application as filed, the phrase "electrostatically associated" means that the organic carrier and antigen are linked, bound or otherwise associated by means which include electrostatic interaction. Thus, "electrostatically associated" reflects a physical property of the claimed complexes, *e.g.*, it is a property of the complexes *per se*. Indeed, in the claimed complex, the electrostatic association involves an ionic bond. Molecules of quillaia saponin contain one mole of glucuronic acid. The ionic state of the –COOH moiety of this sugar confers a single negative charge per molecule. This negative charge attracts positive charges which occur on antigens (due to lysine and arginine molecules in the protein sequence). As a result, an ionic bond is formed between the negatively charged saponin (organic complex) and positively charged sites on the antigen.

That the compositions of Garcon I lack this physical property is evident from their method of manufacture, because adsorbing the antigen to an inorganic carrier (alum) before introducing the organic carrier (MPL/GS21), as taught by Garcon I, precludes the formation of an electrostatic interaction between the organic carrier and antigen, as claimed. This is evident from an analysis of the charge per unit weight of each component, and the relative amount of component (and thus charge) in a typical formulation, such as Example 3 of Garcon I, which contains 20 μg antigen, 50 μg saponin and 500 μg alum.

The following factors are used for the analysis:

(i) The alum is present as $Al(OH)_3$ (see Garcon I, Example 5), which has a molecular weight of 78, and three negative charges and three positive charges per molecule.

(ii) There is approximately one positive charge and one negative charge per 1000 MW of protein. (Assuming that 10 amino acids have MW of 1000, and knowing that proteins generally contain 10% lysine or arginine and 10% aspartate or glutamate, 1 in 10 amino acids will be positively charged and 1 in 10 will be negatively charged.)

(iii) Quillaia saponin has a molecular weight of 2000 and a single negative charge per molecule.

Component	Charge	Unit	Charge/ Unit Wt.	Amount (μg)	Relative amount/dose
$Al(OH)_3$	3+ 3-	78 "	77+ 77-	500	3000+ 3000-
Antigen	1+ 1-	1000 "	2+ 2-	20	1+ 1-
Saponin	1-	2000	1-	50	5-

It is evident from the charge data reflected in the above table that adsorbing the antigen to alum will result in the antigen being completely coated in alum. The alum will surround the antigen, in essence blocking it from subsequently added saponin molecules. Thus, following the Garcon I methodology, there will be no electrostatic association between the antigen and organic carrier, as recited in the instant claims.

Moreover, Example 1 of Garcon I reports that the MPL also is adsorbed to the alum, and Example 2 reports the advantages of binding more of the QS21 to alum. Thus, in the compositions of Garcon I, while there may be an electrostatic association between the inorganic carrier (alum) and the antigen, there is no electrostatic association between the antigen and the organic carrier (MPL/QS21). This physical difference between the claimed invention and the Garcon I compositions precludes anticipation by Garcon I.

The instant claims are further distinguished from Garcon I, because the compositions of Garcon I include alum, which is expressly excluded from the amended claims. (Although Example 3 includes a reference example that does not include alum, the antigen in that particular formulation (gD2t from HSV-2) is an envelope glycoprotein that is expected to have an overall negative charge, and thus is not be expected to form an electrostatic association with saponin, which also is negatively charged.)

For at least these reasons, Garcon I fails to teach a complex or composition meeting every limitation of the rejected claims. Thus, the §102 rejections are improper and should be withdrawn.

III. The Claimed Invention is Non-Obvious

Claims 1, 44-55, 63-76 and 84-85 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Garcon I in combination with Cooper *et al., Immunity*, 10: 439-449 (1999) ("Cooper") and John *et al., Hepatology*, 30(4): 1037-1044 (1999) ("John"). Applicant respectfully traverses these rejections.

As evident from page 4 of the Office Action, the Examiner reads the rejected claims as being directed to "an immunogenic complex comprising an HCV antigen with at least 10 amino acid residues as a T cell epitope and adjuvants including a saponin, and sterol, wherein the organic complex compris[es] saponin and a phospholipid, preferably a phosphoryl lipid A," and finds such a complex to be "generally taught" by Garcon I. Applicants respectfully disagree with this characterization of the claimed invention. For example, it wholly ignores the recitation that the organic complex and antigen are electrostatically associated. Moreover, it does not take into account the claim language excluding alum from the recited complexes and compositions. When the claims are read in their entirety, the non-obviousness of the invention is apparent.

As noted above, Garcon I fails to teach or suggest a complex wherein an organic complex and antigen are electrostatically associated. Moreover, the compositions of Garcon I include alum, which is expressly excluded from the instant claims. Cooper and John are cited for disclosing HCV epitopes *per se*, and do not teach or suggest complexes or compositions according to the invention. Thus, the cited references fail to establish a *prima facie* case of obviousness.

Claims 63 and 85 are further distinguished from the cited references. These claims recite that the complex (claim 63) or composition (claim 85) induces a cytotoxic T-lymphocyte (CTL) response. As explained previously, Garcon I lacks any evidence of the induction of CTLs, and only shows evidence of Th1 responses. While the Examiner cites Figures 1-7 of Garcon I, these figures do not demonstrate the generation of a CTL response. Figures 1 and 5-7 report antibody responses (*e.g.*, antibody titres), Figures 3 and 4 report cytokine induction, and Figure 2 reports antigen-specific cell proliferation.

While the Examiner cites Cruse for stating that "cytokines released by Th1 cells activate CD8+ T cells," it is important to keep in mind that the induction of a peptide-specific CTL response also requires delivery of antigen to the cytosol of an antigen-presenting cell (APC), which is independent of cytokine induction. *See, e.g.*, Cox & Coutler, *Vaccine* 15: 248-58, at 249-50 (1997) (copy attached). As reflected in Table 2 of Cox & Coutler, the induction of a Th1 response does not necessarily correlate with a CTL response. Thus, any evidence that the compositions of Garcon I induce Th1 responses does not indicate that they induce CTL responses, as recited in claims 63 and 85.

Moreover, those skilled in the art would not expect the alum-containing compositions of Garcon I to induce CTL responses. For example, data reported in Stewart *et al.*, *Vaccine* 22: 3738-43 (2004) (copy attached), reveals that that the addition of alum ($Al(OH)_3$) to a vaccine formulation comprising antigen, saponin, and sterol completely abrogated CTL responses (*see, e.g.*, Table 2; compare $Al(OH)_3$/ISCOMATRIX results to ISCOMATRIX results, and note that the $Al(OH)_3$/ISCOMATRIX and $Al(OH)_3$ results are comparable to control). The authors report that the "$Al(OH)_3$ containing preparations . . . did not induce a strong local CTL response," and expressly warn against the use of alum when high CTL responses are desired. Notably, Stewart also reports that the addition of $Al(OH)_3$ reduced, but did not abrogate, Th1 responses (*see, e.g.*, Table 1 and page 3740, last paragraph). Thus, those skilled in the art would not expect Garcon I's compositions to induce CTL responses, not withstanding any apparent ability to induce Th1 responses.

The Examiner criticizes Applicants' previous arguments against Cooper and John, noting that the claims at issue do not recite specific CTL epitopes. Applicants respectfully point out that one advantage of the present invention is that it provides a formulation that is able to achieve CTL responses to a range of HCV antigens by presenting the antigens in the form of an immunogenic complex in which a negatively charged organic complex which comprises a saponin and a sterol is electrostatically associated with a charged antigen which comprises one or more HCV polypeptides. The combination of references cited in the §103 rejection does not teach or suggest such an immunogenic complex. Accordingly, the rejection is improper and should be withdrawn.

IV. Concluding Remarks

Applicants believe that this application is now in condition for allowance, and an early notice to that effect is earnestly solicited.

Should there be any questions regarding this submission, or should any issue remain, the Examiner is invited to contact the undersigned attorney by telephone in order to advance prosecution.

The Commissioner is hereby authorized to charge any additional fees that may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extensions under 37 C.F.R. §1.136 and authorize payment of any extension fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date March 27, 2007

By [signature]
Reg No. 37,288
for Beth A. Burrous
Attorney for Applicant
Registration No. 35,087

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5475
Facsimile: (202) 672-5399